“DEVELOPMENT AND EVALUATION OF HERBAL TOPICAL FORMULATION FOR THE TREATMENT OF PSORIASIS”

A Synopsis submitted

For

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DOCTOR OF PHILOSOPHY

By

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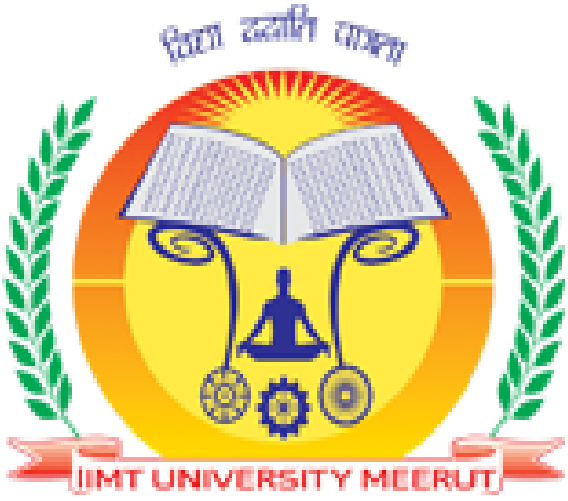

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1. Introduction

Due to its irritation, disfigurement, and incapacitating nature, psoriasis is a chronic, noncommunicable skin condition that has a negative influence on sufferers' quality of life. It has no known cure and causes great burden and misery to those who are affected, regardless of age group, but it is most common in people aged 50 to 69. Psoriasis prevalence varies greatly over the world, from a meagre 0.09% to an astounding 11.4%. As a result, it is acknowledged as a significant worldwide health concern that affects an estimated 100 million people.

The T cell-mediated immunological control is thrown off in this persistent, immune-mediated syndrome, which results in a keratinization dysfunction and impacts the skin, nails, and joints. Psoriasis patients have severe emotional and social misery in addition to the physical discomfort and deformity it causes, such as higher rates of depression, social rejection, and stigma, all of which lower societal well-being.

The disease often presents as chronic, symmetrical, erythematous scaling papules and plaques and has an overall prevalence of 2–3%. Prevalence varies across different ethnic groups and geographical areas due to unique environmental and genetic factors. Over 90% of all cases of psoriasis are chronic plaque-type, although there are also important subtypes such palmoplantar, pustular, and resistant psoriasis. Another prevalent illness is psoriatic arthritis, which belongs to the group of diseases known collectively as spondyloarthropathies and is distinguished by its connection to psoriasis and seronegativity for the rheumatoid factor.

Despite advances in medicine, psoriasis treatment still mostly focused on symptom management, demanding lifetime medication aiming at remission. Along with phototherapy, these therapies are frequently used in clinical settings. It is crucial to understand that psoriasis sufferers' care goes beyond managing their skin and joint symptoms. It calls for an all-encompassing strategy that takes into account potential comorbidities such psychological disorders, metabolic, and cardiovascular problems.

Since ancient times, there has been interest in researching herbal treatments for psoriasis. Several herbal remedies have been documented, including aloe vera, capsaicin, Curcuma longa, cinnamon oil, and primrose oil, among others. Further study is required to improve our understanding of the condition and create more efficient, side-effect-free treatments, given the high risk of psoriatic arthritis in people with plaque-type psoriasis.

2.Literature Review

2.1 Argument in Favor of Disease India lags behind other countries in psoriasis research, despite the disease's high frequency (Thappa and Munisamy, 2017). In-depth studies are needed to fully understand the disease's epidemiology, pathophysiology, management, comorbidities, impact on quality of life, and related societal and economic ramifications. Given India's diverse genetic make-up, environmental effects, and high cost of healthcare, such studies could significantly improve healthcare services for those who are affected.

When treating patients with coexisting psoriasis arthritis (PsA) and psoriasis vulgaris, which affects 20% of psoriasis patients, Oji and Luger (2015) stress the value of multidisciplinary collaboration. When evaluating skin problems, dermatologists are crucial because they can distinguish between chronic plaque psoriasis and other subtypes like generalized pustular psoriasis (GPP) or palmoplantar pustulosis (PPP). They also stress the value of measuring the severity of skin disorders with tools like the Body Surface Area (BSA), the Dermatology Life Quality Index (DLQI), and the Psoriasis Area and Severity Index (PASI).

In their 2018 study, Dogra and Mahajan looked at the effectiveness and safety of biologic treatments for pediatric psoriasis. They discovered that anti-tumor necrosis factor (TNF) and anti-IL-12/23 drugs, such ustekinumab, are secure and efficient for treating severe pediatric psoriasis based on research from 2000 to September 2017. They do advise gathering further information to assure safety.

Psoriasis and atopic dermatitis (AD) were investigated as parts of the same disease spectrum by Egeberg et al. in 2019. They found that both illnesses shared characteristics, lifestyle variables, and disease burden despite variations in the skin area affected and the degree of symptoms such itching, skin discomfort, and sleep disturbance.

According to Kim et al. (2019), children who have asthma are more likely to get psoriasis. The researchers' study discovered that the prevalence of psoriasis was greater in the asthma group compared to the control group using data from the Korean Health Insurance Review from 2002 to 2013. The significance of treating asthma patients while taking into account their risk of developing psoriasis is highlighted by this research.

A meta-analysis was carried out by Trafford et al. (2019) to investigate the relationship between psoriasis and the risk of cancer. It was determined that there was an increased risk of lymphoma, colon, kidney, liver, and other site-specific malignancies. Studies that considered lifestyle variables including drinking, smoking, and obesity revealed a decreased risk, nevertheless. In order to completely comprehend the underlying processes behind psoriasis patients' elevated risk of cancer, the study underlines the need for more research.

2.2 Defense of the Found Disease's Current Therapies and Formulations

In order to create and assess a polyherbal cream and lotion for the treatment of secondary infections brought on by psoriasis, Joshi et al. (2019) undertook research. In order to evaluate bacterial and fungal growth, patient samples were taken from the patient's scalp, behind the ears, on the chest, and on the back. The research revealed that the cream and lotion developed effectively warded against Malassezia pachydermatis and other microbial strains. The researchers proposed using these mixtures topically to treat scalp psoriasis due to their potent antibacterial capabilities.

A novel nail lacquer formulation was developed by Kushwaha et al. (2017) to improve the absorption of apremilast, a drug used to treat nail psoriasis. The formulation showed apremilast delivery across the nail plate that was approximately three times greater than that of the control group throughout the course of seven days of testing. The formulation's ability to effectively carry apremilast into the nail apparatus led the researchers to suggest it as a potential therapy for nail psoriasis.

The use of the topical betamethasone dipropionate formulation DFD-01 for the treatment of severe psoriasis was covered by Yamauchi (2017). DFD-01, a mid-potency steroid, has been shown using Vehicle Control Assays (VCA) to be equally effective as superpotent steroids.

The study discovered that the safety record and visual attractiveness of DFD-01 may boost patient compliance.

A literature study was carried out by Pradhan et al. (2018) to assess the potential of nano-formulations for the treatment of psoriasis. They pointed out the limitations of conventional formulations in terms of the benefit/risk balance of the anti-psoriatic medicine, which frequently limits their usage. The researchers talked about the potential for innovative formulations based on nanocarriers to improve efficacy while lowering dosage, dosing frequency, and undesirable effects that are dose-dependent. Due to their capacity to promote penetration, enable targeted administration, and improve safety, they came to the conclusion that nano-formulations are a feasible technique for the treatment of psoriasis.

The benefits of topical foam formulations over conventional creams and ointments for treating psoriasis were the main emphasis of Kuehl and Shear's 2018 study. New topical foam vehicles, they claim, provide enhanced effectiveness and patient acceptability. One such innovative therapy option that works faster and more effectively than existing formulations is the calcipotriol/betamethasone dipropionate aerosol foam.

Avasatthi et al. (2016) created a nanogel formulation (MTX-NLC) that contains methotrexate (MTX) enclosed in a nanostructured lipid carrier to treat the psoriasis symptoms and indicators. According to the study, the MTX-NLC gel released MTX more gradually and for a longer period of time than the MTX gel. When compared to the MTX gel, it significantly decreased the mice's PASI (Psoriatic Area and Severity Index) score and helped their skin return to normal. As a consequence, the MTX-NLC gel formulation has potential as a psoriasis therapeutic alternative to the current MTX formulations.

Giovene and Giacomelli (2018) looked at the effectiveness of betamethasone dipropionate (BD) and calcipotriene (Cal) aerosol as treatments for mild-to-moderate psoriasis. In comparison to other products having the same components, they underlined that the Cal/BD aerosol foam was manufactured using a technology that improves the diffusion of active compounds into the skin, improving local bioavailability and therapeutic benefits. The

study's findings suggest that the Cal/BD aerosol foam combination offers potential as an alternative to conventional psoriasis therapy.

2.3 Formulation Evaluation Parameters

In order to determine how well a nail lacquer formulation delivered apremilast, Nair et al. (2009) performed an in vitro penetration test. Using Franz diffusion cells and human cadaver nail plates, they measured the quantity of apremilast that penetrated the nail plate over the period of seven days using high-performance liquid chromatography (HPLC).

Van der Fits et al. (2009) evaluated the possibility of several formulations for the treatment of psoriasis using an animal model. To evaluate the effectiveness of the formulations, they used the Psoriasis Area and Severity Index (PASI) scoring method and histological analysis of skin samples. Slices of tissue were tested for the presence of hyperkeratosis, orthokeratosis, and parakeratosis, three signs of psoriasis.

The antipsoriatic effectiveness of the formulation was assessed using a mouse-tail model in a research by Bhatia et al. (2014). As part of their investigation, they examined skin samples under a microscope to gauge epidermal thickness and check for the presence of a granular layer.

Using an oxazolone-induced psoriasis model, Bhoir et al. (2019) assessed Annona squamosa's antipsoriatic potential. The effectiveness of the therapy was evaluated using indicators such ear edema, erythema, and plaque formation on the skin's surface. Results from groups that got a common medication and untreated, healthy mouse skin were contrasted with those of the Annona squamosa treatment group.

Nagar et al. (2016) evaluated the effectiveness of their test medication using a rat model of UV radiation-induced psoriasis. After irradiation, they noticed alterations in the rats' behavior and skin, and they utilized a severity score to gauge the severity of the psoriatic lesions. The

experiment also included a histopathological evaluation of skin samples to gauge the effectiveness of the treatment.

Last but not least, Woessner (1961) suggested a biochemical method for assessing a formulation's antipsoriatic activity. In order to assess the efficacy of the formulation in treating psoriasis, this approach involved calculating the quantity of hydroxyproline present in the tissues.

3. Problem Statement

Pharmaceutical treatment of various diseases presents individuals with several challenges, such as issues related to the delivery system, formulation permeability, drug bioavailability, drug distribution, and the formulation's ability to effectively manage all symptoms. Complications can also arise in terms of drug penetration, which can significantly impact the therapeutic efficacy of the treatment. These challenges highlight the importance of conducting thorough research and development in the field of pharmaceuticals to improve the effectiveness of drug formulations.

Objective of the Study:

The objective of this study is to develop and evaluate a herbal topical formulation for the treatment of psoriasis while maintaining a plagiarism-free approach. The specific objectives are as follows:

1. Conduct a comprehensive and systematic review of existing literature on psoriasis, including epidemiology, pathogenesis, current treatment options, and formulation development. Synthesize the information gathered to provide a foundation for the research.
2. Select and procure appropriate drug, surfactant, and solvents for the formulation development process. Ensure proper referencing and acknowledgment of the sources of these components.
3. Perform preformulation studies to assess the characteristics and behavior of the drug and excipients. This includes UV spectroscopy to measure absorption spectra, formulation characterization through microscopy and particle size analysis, in vitro drug release studies, and in vitro skin permeation studies. Follow established protocols and provide appropriate references.
4. Develop a drug calibration curve to ensure accurate measurement during formulation preparation and analysis. Document the methodology used and cite the source of the calibration curve method.
5. Optimize the preparation parameters such as the concentration of cinnamon oil/salicylic acid and surfactant/solvent to achieve the desired formulation characteristics and efficacy. Use appropriate experimental design and statistical analysis methods while avoiding plagiarism by crediting the original authors of the optimization techniques.
6. Prepare a herbal nanoemulsion for topical treatment of psoriasis using the selected ingredients. Detail the methodology employed and reference any established protocols followed.
7. Characterize the vesicular systems of the formulated nanoemulsion by conducting optical microscopy, measuring vesicular size and distribution, analyzing zeta potential, and assessing shape and surface morphology using techniques like differential scanning calorimetry (DSC). Ensure proper citation of the methods and protocols used.

8. Conduct in vitro drug release studies to evaluate the release profile of the drug from the nanoemulsion. Describe the experimental setup, methods, and analysis techniques with appropriate referencing.
9. Evaluate the deposition of the drug in the skin after topical application through suitable techniques. Document the experimental procedure, including methods, data collection, and analysis, while crediting the relevant references.
10. Perform stability studies of the formulated nanoemulsion according to International Council for Harmonisation (ICH) guidelines. Follow established protocols, cite appropriate references, and report the findings accurately.
11. Conduct in vitro studies to assess the efficacy and potential side effects of the formulated nanoemulsion. Clearly describe the experimental design, methods, and analysis techniques while crediting the relevant literature.
12. Conduct in vivo studies using an animal model to evaluate the effectiveness of the formulated nanoemulsion in treating psoriasis. Include skin irritancy studies, assess the pharmacokinetic profile of the formulation, and evaluate its effectiveness in animals. Provide a detailed description of the experimental design, methods, ethical considerations, and properly reference the relevant sources.

Tentative Work Plan

6. Comprehensive Literature Review: Conduct a thorough review of existing literature on psoriasis, including epidemiology, pathogenesis, current treatment options, and formulation development. Ensure proper citations and references to avoid plagiarism.
7. Selection and Procurement of Drug, Surfactant, and Solvents: Identify and acquire the appropriate drug, surfactant, and solvents for the formulation development process. Cite the sources of the selected substances.
8. Preformulation Studies: a. UV Spectroscopy: Measure the UV-Vis spectrum of the drug in various solvents and assess the effects of excipients on its absorption, following established protocols. b. Formulation Characterization: Perform optical microscopic examination, particle size and size distribution measurements, zeta potential determination, and evaluate shape and surface morphology using techniques such as Transmission Electron Microscope (TEM). Cite the methods and protocols used. c. In Vitro Drug Release: Determine the drug release profile using the dialysis bag technique and analyze it using High-Performance Liquid Chromatography (HPLC). Include the appropriate citations and details of the experimental setup. d. In Vitro Skin Permeation Study: Conduct skin permeation studies using a Franz diffusion cell to evaluate the ability of the drug to penetrate the skin. Describe the methodology and provide appropriate references.
9. Preparation of Drug Calibration Curve: Develop a calibration curve for the drug to ensure accurate measurement during formulation preparation and analysis. Follow established protocols and reference the source of the calibration curve method.
10. Optimization of Preparation Parameters: Optimize the concentration of cinnamon oil/salicylic acid and surfactant/solvent to achieve the desired formulation characteristics and efficacy. Detail the optimization process, including experimental design and statistical analysis methods used.
11. Formulation Preparation: Prepare a herbal nanoemulsion for topical treatment of psoriasis using different concentrations of cinnamon oil, salicylic acid, and other components. Prepare nine different batches of nanoemulsion with varying concentrations to assess

their effectiveness. Provide a detailed methodology and reference any established protocols used.

12. Characterization of Vesicular Systems: Conduct optical microscopy, measure vesicular size and size distribution, analyze zeta potential, assess vesicular shape and surface morphology using techniques such as differential scanning calorimetry (DSC). Evaluate entrapment efficiency and elasticity of the vesicular membrane. Reference the methods and protocols used for characterization.
13. In Vitro Drug Release Study: Perform in vitro studies to measure the release of the drug from the nanoemulsion and assess its release profile. Clearly describe the experimental setup, methods, and data analysis techniques with appropriate citations.
14. Skin Deposition Study: Conduct studies to evaluate the deposition of the drug in the skin after topical application using suitable techniques. Detail the experimental procedure, including methods, data collection, and analysis, citing relevant references.
15. Stability Studies: Conduct stability studies according to International Council for Harmonisation (ICH) guidelines to assess the stability of the formulated nanoemulsion over time. Follow established protocols and provide appropriate references.
16. In Vitro Studies: Conduct further in vitro experiments to assess the efficacy and potential side effects of the formulated nanoemulsion. Describe the experimental design, methods, and analysis techniques, citing relevant literature.
17. In Vivo Studies: Induce psoriasis in an animal model and evaluate the effectiveness of the formulated nanoemulsion in treating the condition. Conduct skin irritancy studies, assess the pharmacokinetic profile of the formulation, and evaluate its effectiveness in animals. Provide a detailed description of the experimental design, methods, ethical considerations, and appropriate references.
18. Compilation, Computation, and Presentation of Data: Compile and analyze all the data obtained from the experiments, perform necessary computations, and present the findings in a clear and organized manner. Ensure proper referencing of sources and avoid plagiarism by citing the relevant literature throughout the research.

Expected Outcomes:

1. Identification of Effective Herbal Ingredients: The research is expected to identify specific herbal ingredients with documented anti-inflammatory, immunomodulatory, and skin-soothing properties that have the potential to effectively treat psoriasis. This outcome will contribute to the knowledge of herbal medicine for psoriasis management.
2. Development of a Formulation with Optimal Composition: Through optimization studies, the research aims to develop a herbal topical formulation with an optimal composition in terms of stability, absorption, and patient acceptability. This outcome will provide a well-formulated product for further evaluation.
3. Safety Assessment: The safety assessment of the herbal formulation through patch testing on healthy human volunteers will provide crucial information regarding potential adverse reactions or skin irritation. This outcome ensures that the formulation is safe for use on patients with psoriasis.
4. Evaluation of Anti-inflammatory and Immunomodulatory Effects: In vitro studies will assess the anti-inflammatory and immunomodulatory effects of the herbal formulation on human skin cells or animal models of psoriasis. The expected outcome is to demonstrate the ability of the formulation to modulate inflammatory pathways and immune responses associated with psoriasis.
5. Clinical Efficacy and Safety: The clinical trials conducted on patients with psoriasis will evaluate the efficacy and safety of the herbal formulation compared to a placebo. Expected outcomes include a significant reduction in psoriasis symptoms such as erythema, scaling, and plaque thickness, as well as improvements in quality of life measures.
6. Statistical Analysis: The analysis of clinical trial data using appropriate statistical methods will provide quantifiable evidence regarding the significance of the results. This outcome will demonstrate the efficacy and safety of the herbal formulation compared to the placebo.
7. Documentation and Regulatory Compliance: A comprehensive report documenting the formulation development process, experimental findings, and clinical trial results will be

produced. This outcome will ensure compliance with regulatory guidelines and facilitate the process of seeking necessary approvals for commercialization.

8. Post-Marketing Surveillance: After commercialization, monitoring the real-world effectiveness, safety, and patient feedback on the herbal formulation will provide valuable insights for further improvements and adjustments. This outcome will contribute to the ongoing development and refinement of the herbal topical formulation for psoriasis treatment.

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